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CYTOXAN

Cyclophosphamide (Cytoxan - Mead Johnson) is offered as a "new, potent cytotoxic agent" for the palliative therapy of such malignant disorders as Hodgkin's disease, lymphosarcoma, giant follicular lymphomas, reticulum cell sarcoma, acute and chronic leukemia, mycosis fungoides and some solid carcinomas. This drug is an alkylating agent related to the nitrogen mustards, but it is claimed to be both more effective and less toxic than the nitrogen mustards.

The number of cases reported thus far is too small to permit a meaningful comparison of the relative therapeutic effectiveness of Cytoxan and other chemical cytotoxic agents such as chlorambucil (Leukeran - Burroughs, Wellcome), Triethylene Melamine (TEM - Lederle), nitrogen mustard (Mustargen - Merck), triethylene thiophosphoramide (Thio-TEPA - Lederle), and busulfan (Myleran - Burroughs, Wellcome). The claim of greater effectiveness is based largely on animal studies of the effects of Cytoxan and other agents on transplanted tumors. Such evidence has little significance, however; other drugs have appeared more effective than nitrogen mustard in animal studies without showing greater effectiveness in clinical use.

RELATIVE EFFECTIVENESS - On the basis of limited clinical and experimental evidence (M. Lane, p. 1, and J. M. Venditti, et al., p. 6 of Cancer Chemotherapy Reports, USPHS No. 3, June, 1959, and the reference cited below), Cytoxan cannot be considered clearly superior to nitrogen mustard either in therapeutic range or in effectiveness against particular neoplasms. It has not been shown to be effective when other alkylating agents no longer produce a palliative response. Despite the manufacturer's recommendation, there is no clear indication for the use of Cytoxan in acute leukemia. Although Cytoxan does have a palliative effect in some cases of solid carcinomas, for example, carcinoma of the breast, uterus and ovary (R. G. Ravdin, et al., Proc. Am. Assoc. for Cancer Res., 3:55, 1959), it remains to be proved that Cytoxan is more useful in this respect than other alkylating agents.

Cytoxan, like other alkylating agents, can cause increased susceptibility to infection, nausea and vomiting, leukopenia, and thrombocytopenia. Cytoxan also causes alopecia much more frequently than other alkylating agents (nitrogen mustard causes none). Although alopecia from Cytoxan is reported to be reversed on cessation of treatment, it is a matter of serious concern to patients, especially

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women, in whom treatment for long periods may be indicated. Evidence presented by the manufacturer indicates that leukopenia caused by ordinary doses of Cytoxan is accompanied by relatively little depression of the platelet count. But large doses of Cytoxan can produce thrombocytopenia.

DOSAGE - The manufacturer recommends intravenous infusions in the adult of 2 to 8 mg./kg. daily for at least six days initially, with dosage schedules and subsequent courses depending upon the type of neoplasm and the patient's bone-marrow state (determined by frequent platelet and white blood counts). The initial treatment course must be somewhat arbitrary with no further treatment until after evaluation at least a week later. Like other agents, Cytoxan should not be given to patients with severe leukopenia or thrombocytopenia. Cytoxan is available in oral as well as parenteral form; in the absence of sufficient data, oral dosage must be considered as still in the investigational stage.

In summary, Cytoxan is similar to nitrogen mustard and other alkylating agents in palliative effects on malignant tumors. If initial studies are confirmed, it may be somewhat safer than other alkylating agents with respect to blood platelet depression. The main disadvantage emerging from published preliminary clinical studies is the very high incidence of alopecia. It is also much more costly than other alkylating agents. (The cost to the physician of a dozen 200-mg. ampules would be about $40.)

VASOPRESSOR DRUGS FOR SHOCK

Acute arterial hypotension, or shock, is a symptom and not a disease, and wherever possible the underlying causes must, of course, be corrected. But when the causes are obscure or not immediately correctable, or when the duration of the shock is unpredictable (as in myocardial infarction or spinal anesthesia) the doctor may have to rely on vasopressor drugs to prevent irreversible tissue damage. Many vasopressor agents are available, and some of the more important ones will be discussed in future issues. This discussion is intended to provide useful background material, and to show that the choice of a particular agent is not always so critical as the promotion material sometimes suggests.

MODE OF ACTION - All vasopressor drugs used in the treatment of shock are sympathomimetic amines and are administered parenterally. Some raise the blood pressure by causing peripheral vasoconstriction; phenylephrine HCl (Neo-Synephrine - Winthrop) and methoxamine (Vasoxyl - Burroughs, Wellcome) act in this way. Others have a positive inotropic effect, causing cardiac stimulation as well as peripheral dilatation. Among these are methamphetamine (Desoxyn - Abbott; Drinalfa - Squibb; Methedrine - Burroughs, Wellcome) and mephentermine (Wyamine - Wyeth). Still others are both cardiac stimulators and peripheral vasoconstrictors. Of those currently offered for the treatment of shock, levarterenol or norepinephrine (Levophed - Winthrop) and metaraminol (Aramine - Merck) act mainly by vasoconstriction.

Vasopressors are used not to raise blood pressure, but to improve blood flow through tissues and organs, particularly the heart, the brain and the kidney.

Blood pressure is not a reliable index of the adequacy of peripheral or organ blood flow. Elevated blood pressure, when it is accompanied by intense vasoconstriction, may result in lower tissue blood flow than slightly subnormal blood pressure accompanied by vasodilatation. One study showed a decrease of as much as 20 per cent in cerebral blood flow in normal subjects after a 20 to 30 per cent increase in blood pressure obtained with Levophed; on the other hand, a dose of epinephrine which raised mean arterial blood pressure very little increased cerebral blood flow by as much as 20 per cent (B. D. King, et al., J. Clin. Invest., 31:273, 1952).

CLINICAL EXPERIENCE - Such findings would seem to indicate a rather clear choice among drugs, but clinical experience says otherwise. For example, the hypotension of myocardial infarction is characterized by reduced cardiac output and increased peripheral resistance (F. D. Fries, et al., J. Clin. Invest., 31:131, 1952), and in such cases, the ideal drug would seem to be one like Wyamine or methamphetamine, which give both cardiac stimulation and peripheral vasodilatation. Clinical experience shows, however, that such drugs as Levophed and Aramine, which act mainly by peripheral vasoconstriction, are also effective.

To take another example, acute hypotension associated with spinal anesthesia or the use of ganglion blockers is due to both arterial dilatation (which lowers peripheral vascular resistance) and venous dilatation (which decreases venous return to the heart and so decreases cardiac output). In this type of hypotension, as might be predicted, pure peripheral vasoconstrictors, such as Vasoxyl and Neo-Synephrine, are effective. Clinical trials show, however, that Wyamine and other agents which lack a vasoconstrictor effect are also effective (D. M. Aviado, Jr., Anesthesiology, 20:71, 1959; Circulation Research, 7:815, 1959).

In some conditions a vasopressor alone may have no effect on blood pressure. These include shock due to contraction of blood volume in severe dehydration, to adrenal cortical insufficiency, and to the hypotension sometimes caused by tranquilizers, especially when they are combined with narcotics or anesthetics. Vasopressors are often helpful in traumatic shock or in shock due to acute blood loss, burns, or severe infections, particularly when combined with other measures.

No vasopressor is perfect; each has advantages and disadvantages. Differences in ease of administration and dosage, duration of effect, tendency to cause tachyphylaxis and side effects, and effect on myocardial irritability and rhythmicity must, of course, be considered in the choice of a drug, and such differences will be discussed in appraisals of the individual drugs. From a practical point of view, it is better for the physician to become familiar with one or two agents than to skip from one to another to obtain theoretical advantages.

ARTHROPAN

Choline salicylate (Arthropan Liquid - Purdue, Frederick) is a new, highly-soluble salicylate. It is offered chiefly as a substitute for aspirin in the treatment of arthritis, with the claim that it provides "rapid anti-inflammatory ac-

tion"; but its cost - about 10 times the cost of equivalent dosage of aspirin - will generally rule out its use except where the arthritis patient cannot tolerate aspirin (or sodium salicylate, which is also highly soluble).

SPEED OF ABSORPTION - High salicylate blood levels and hence anti-inflammatory effects are, as claimed, achieved faster with Arthropan than with aspirin. The therapeutic significance of the difference appears to be very limited, however, since repeated salicylate dosage is the rule with arthritis, and since adequate (2-gram) anti-inflammatory doses of aspirin or sodium salicylate give sustained plasma levels of salicylate for over 8 hours (P. K. Smith, et al., J. Pharmacol., 87:237, 1946). The implication in Arthropan literature that it takes nearly two hours to get effective blood levels with aspirin is not supported by clinical studies. In two studies (R. C. Batterman, N.E. J. Med., 258:213, 1958; G. A. Cronk, N.E. J. Med., 258:219, 1958), effective blood levels were reached in less than 60 minutes with aspirin. Even faster absorption of aspirin is achieved if it is taken with one or two grams of bicarbonate of soda and water (D. Lester, J. Pharmacol., 87:329, 1946). Repeated administration of sodium bicarbonate, on the other hand, will depress salicylate blood levels by promoting renal excretion (see P. K. Smith, et al., cited above). (But note that the amount of alkaline agents in "buffered aspirin" is too small to affect either absorption or excretion appreciably.)

It is claimed that Arthropan gives analgesic effects more rapidly than aspirin. Like sodium salicylate, however, Arthropan is a much less satisfactory analgesic than aspirin, the analgesic effect of which apparently depends on the presence in the blood and tissues of unhydrolyzed acetylsalicylic acid.

GASTROINTESTINAL BLEEDING - As with Calurin, a new soluble aspirin preparation (see The Medical Letter, Feb. 5, 1960), the main question about Arthropan is whether it causes less gastrointestinal bleeding than ordinary aspirin. Some evidence that it does cause less bleeding was presented by R. N. Pierson, et al., in a talk before the Eastern Section of the American Federation for Clinical Research, on December 11, 1959, but confirming evidence is needed. If the results are confirmed, then a soluble salicylate such as Arthropan or sodium salicylate may be preferable to aspirin for those patients in whom prolonged administration of large doses of aspirin causes gastrointestinal bleeding (patients with peptic ulcer, for example). It should be noted, however, that taking aspirin with plenty of water or after meals can be expected to reduce the tendency to bleeding. It has not been established that other gastrointestinal side effects, such as nausea, vomiting or heartburn, are less common with Arthropan than with aspirin.

A soluble salicylate offers advantages to those unable to swallow pills, but such patients can resort to less expensive effervescent aspirin tablets such as Alka Seltzer, or to crushing the aspirin tablets into a powder and mixing it with jam or honey; or for anti-inflammatory effects, to sodium salicylate.

In summary, Arthropan is an acceptable soluble salicylate but, except where sodium restriction is necessary, it has no advantage over the older soluble salicylate, sodium salicylate.

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